

REMARKS

Claims 1-38 and 40-43 are pending and under examination in this application. New claims 44-50 have been added, support for which can be found in the specification including, for example, at page 12, lines 25-30. Claim 28 has been amended to correct an obvious error. Accordingly, the amendments do not raise any issues of new matter and entry of the amendments is respectfully requested. Following entry of the amendments claims 1-38 and 40-50 will be under examination.

Applicants have reviewed all grounds of rejection issued in the Office Action mailed February 21, 2006, and respectfully traverse for the reasons that follow. Further, Applicants respectfully disagree with the Office's proffered rebuttal in the Advisory Action mailed May 1, 2006, of Applicants' arguments filed April 14, 2006. Applicants reassert their arguments of record and respectfully request reconsideration.

Claims 1-16, 22-27 and 31-42 stand rejected under 35 U.S.C. § 103(a) as being obvious over Rothberg et al., U.S. Patent No. 6,274,320, in view of Walt et al., U.S. Patent No. 6,327,410, the Office alleging that it would have been obvious to one skilled in the art to use the microspheres of Walt et al. distributed over the surface of a fiber optic sensor in the sequencing method of Rothberg et al. allegedly because Walt et al. provide a method of generating large fiber optic arrays and because bead-based chemistry systems allow synthesis of bioactive agents to be separated from their placement on an array. (e.g., see Office Action mailed Nov. 28, 2005 at pp.10-11, and Advisory Action mailed May 1, 2006 at p.2). The Office attempts to clarify the alleged motivation by stating:

Therefore, it is clear that there is a very strong motivation to use beads on a fiber optic surface since this allows for fast generation of large fiber optic arrays.

Advisory Action mailed May 1, 2006, at p.2.

However, the question is not whether motivation exists to use beads on a fiber optic surface. Walt et al. describes such a use. Rather, the question is whether:

[O]ne of ordinary skill in the art at the time of the invention [would have been motivated to use] the microspheres of Walt et al. distributed over the surface of the fiber optic sensor in the method of nucleic acid sequencing of Rothberg et al.

Office Action mailed Nov. 28, 2005, at p.10 (emphasis added).

As the rejection stands, the Office has failed to articulate a *prima facie* case of obviousness because the motivation, teaching or suggestion has been completely omitted. The “mere identification in the prior art of each element is insufficient to defeat the patentability of the combined subject matter as a whole.” *In re Kahn*, Case No. 04-1616, slip op. at 11 (Fed. Cir. March 22, 2006) (citing *In re Rouffet*, 149 F.3d 1350, 1355, 1357 (Fed. Cir. 1998)). As articulated, the mere mention of using beads on a fiber optic surface fails to provide the proper motivation to combine because it does nothing more than identify one element of the claim. (Advisory Action mailed May 1, 2006, at p.2).

With respect to the Office’s original articulation of this rejection, Applicant maintains that any teaching, suggestion or motivation to combine Rothberg et al. with Walt et al. is lacking because Rothberg et al. teach away from such a combination.

To establish a *prima facie* case of obviousness based upon a combination of elements across different references, the law requires that “at the time the invention was made” (35 U.S.C. § 103; *In re Kahn*, Case No. 04-1616, slip op. at 12) “there be a suggestion, motivation or teaching to those skilled in the art for such a combination.” *Iron Grip Barbell, Co. v. York Barbell, Co.*, Case No. 04-1149, slip op. at 5 (Fed. Cir. December 14, 2004) (citing *In re Fine*, 837 F.2d 1071, 1074 (Fed. Cir. 1988)). This requirement prevents the use of “the inventor’s disclosure as a blueprint for piecing together the prior art to defeat patentability - the essence of hindsight.” *Id.*; see also *In re Kahn*, Case No. 04-1616, slip op. at 12. Obviousness can be rebutted where it is shown that the prior art taught away from the claimed invention. *Iron Grip Barbell, Co.*, Case No. 04-1149, slip op. at 7 (citing *In re Geisler*, 116 F.3d 1465, 1471 (Fed. Cir. 1997)).

The invention is directed to a method of sequencing a plurality of target nucleic acids that includes providing an array having a substrate with discrete sites, a population of microspheres having at least first and second subpopulations and an enzyme for generating a pyrophosphate signal attached at the discrete sites. Simultaneously extending first and second primers and

detecting the release of pyrophosphate (PPi) within a common reaction chamber to determine the sequence of the plurality of target nucleic acids.

Rothberg et al. teach away from any teaching, suggestion or motivation to combine the sequencing method described therein with the microsphere containing array described by Walt et al. Rothberg et al. explicitly point to reported problems associated with the use of pyrophosphate sequencing in combination with beads because bead loss was a limiting factor (e.g., see Applicant's Response filed December 19, 2005, at p.11). Based on the above and other descriptions in Rothberg et al., the combination of pyrophosphate sequencing with microspheres was undesirable, limited and inapplicable to pyrophosphate sequencing strategies (e.g., see *Id.* at p.11-12).

The Office also now appears to contend that any teaching away in Rothberg et al. from using beads in solution "miss[es] the point of the fact that . . . beads are immobilized in the wells" in the microarray of Walt et al (e.g., see Advisory Action at p.2, para. 4). Applicant is aware that the Office alleges Walt et al. describe the use of beads immobilized in the wells of an array (e.g., see Office Action mailed February 21, 2006, at p.4, para.2). However, the mere identification of an element in a publication is insufficient motivation to combine references. *In re Kahn*, Case No. 04-1616, slip op. at 11.

"The 'motivation-suggestion-teaching' requirement protects against the entry of hindsight into the obviousness analysis," *In re Kahn*, Case No. 04-1616, slip op. at 12. In the motivation analysis, the problem examined is "the general problem that confronted the inventor before the invention was made." *In re Kahn*, Case No. 04-1616, slip op. at 15 (citing *Cross Med. Prods., Inc. v. Medtronic Sofamor Danek, Inc.*, 424 F.3d 1293, 1323 (Fed. Cir. 2005)). However, "[d]efining the problem in terms of its solution reveals improper hindsight in the selection of the prior art relevant to obviousness." *Ecolchem, Inc. v. S. Cal. Edison Co.*, 227 F.3d 1361, 1372 (Fed. Cir. 2000) (internal citation omitted) (quoting *Monarch Knitting Mach. Corp. v. Sulzer Morat GmbH*, 139 F.3d 877, 881 (Fed. Cir. 1998)).

One problem facing the inventor solved by the claimed invention is directed to overcoming the negative effects of PPi diffusion on signal detection and resolution when using an array surface. There is nothing in the cited art which provides the motivation to arrive at the

claimed invention as a solution to this problem facing the inventor. *Id.* Hence, the Office's conclusion appears to be a hindsight reconstruction which ignores a teaching away in the art.

Applicant has pointed to the descriptions in Rothberg et al. that teach away from using beads in a microarray (e.g., see Applicant's Responses dated December 19, 2005, at pp.11-12, and April 14, 2006, at pp.10-12). In reciting several possible alternatives to this problem, Rothberg et al. failed to mention the use of microspheres or even microspheres in wells as a possibility to reduce PPI diffusion (e.g., see Applicant's Responses dated December 19, 2005, at pp.11-12, and April 14, 2006, at pp.12-14).

Applicant has shown that the solution in Rothberg et al. to the inventor's problem, pointed to by the Office as intended to address bead loss when used as a support, was directed to making cavities of at least 50 μm in depth (e.g., see Applicant's Response dated April 14, 2006, at pp.12-13). Therefore, Rothberg et al. describes resolving the inventor's problem by creating a physical separation of samples using deep cavities to prevent diffusion of PPI prior to detection, not to making cavities and placing beads in the cavities (e.g., see Applicant's Responses dated December 19, 2005, at pp.11-12, and April 14, 2006, at pp.12-14).

Rothberg et al., although aware of Walt's optical sensor arrays, chose to cite site Walt's work, Michael et al., for describing a method of acid-etching cavities, not for a method of acid-etching to place beads in the cavities for use as a support (e.g., see Applicant's Response dated April 14, 2006, at pp.12-13). Walt et al. does not address the problem facing the inventor of diminished detection and signal resolution for array surface formats due to PPI diffusion.

Accordingly, Rothberg et al. does not teach or suggest placing beads in wells. Rather, Rothberg et al. describes making cavities that physically prevent lateral diffusion of released pyrophosphate (PPI) from the sequencing reaction. Walt et al. can be viewed as nothing more than merely identifying an element because Walt et al. is directed to making arrays without concern for detecting diffusible substrates on such arrays. Therefore, Rothberg et al. was faced with a similar problem as the inventor of the subject application, but chose to teach away from using beads as an array support in pyrophosphate sequencing reactions. The mere identification of using beads by Walt et al. does not overcome this teaching away.

Applicant maintains that the claimed invention is unobvious over the cited art to Rothberg et al. and Walt et al. The current rejection fails to articulate a *prima facie* case of obviousness because the motivation, teaching or suggestion has been completely omitted. The factual analysis has been incorrectly applied to the solution of the inventor's problem rather than to the problem itself. The factual analysis also has been incorrectly applied to the motivation analysis rather than to Applicant's rebuttal that Rothberg et al. teaches away from the claimed invention. Applicant maintains that they have met their burden and that a finding of allowability should be rendered.

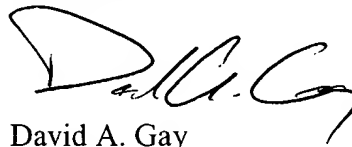
CONCLUSION

In light of the Amendments and Remarks herein, Applicants submit that the claims are in condition for allowance and respectfully request a notice to this effect. Should the Examiner have any questions, she is invited to call the undersigned attorney.

To the extent necessary, a petition for an extension of time under 37 C.F.R. 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 502624 and please credit any excess fees to such deposit account.

Respectfully submitted,

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